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DESCRIPTION

The instant invention concerns new salts of the 6-Chlor-u-methylcarbazol-2-essigsäure with a basic A aminocarbonic acid, in particular to the use as anti-inflammatory, analgetische and anti-rheumatoid agents, a method to the preparation of these salts, pharmaceutical preparations on the basis of these salts and the use of these salts to the preparation of antiinflarnmatorischen, analgetischen and anti-rheumatoid agents.

In particular the invention concerns the salts of the rac-6 chlorine A methylcarbazol 2-essigsäure (appended as Carprofene referred) with a natural occurring basic A-aminocarbonic acid. Prefered ones are the salts with L lysine or L arginine, as carprofene L lysinat.

Except lysine and arginine histidine and ornithine can become as basic A-aminocarbonic acids mentioned.

The salts according to invention can become by the fact prepared that one converts the 6-Chlor-a-methylcarbazol 2-essigsäure with a basic A-aminocarbonic acid in a solvent.

One knows a solution or a suspension of the 6-Chlor-amethylcarbazol 2-essigsäure (the appended acidic one mentioned) or the basic arAminocarbonsäure with a solution or a suspension of the basic A-aminocarbonic acid and/or. the acidic ones shift. The acidic one and the A become aminocarbonic acid in equimolar or a ratio used different of it. The developed salt can as Kristallisat. Lyophilisat or in solution isolated become.

When one can use solvents for the acidic one or several Niederalkanole or mixtures of it with halogenated hydrocarbons and/or with ethers, and for the A-aminocarbonic acids toluene or, preferably, waters or mixtures of it with Niederalkanolen and/or ethers. Examples of Niederalkanolen are methanol and ethanol of halogenated hydrocarbons Methy lenchloridz and of ethers tetrahydrofurane (THF).

Depending upon composition of the solvent mixture the salt direct, or after restricting the solution, precipitates or after addition of an inert solvent. Alternative one knows the salt as distillation residue, which one crystallizes and/or. to recrystallize, recovered can become. As solvents one can use here Niederalkanole or waters, or mixtures of it with ethers or a mixture of toluene with a Niederalkanol.

The appropriately made crystallization with a temperature between -20 and + 50 °C, preferably between 0 C and room temperature (blank), in particular with blank, and restricting a brine with normal pressure or reduced flruck bel a temperature between 0 and 50 °C and bottom agitations.

The salts according to invention have anti-inflammatory, analgetische and anti-rheumatoid effect and can thus as anti-inflammatory, analgetische and anti-rheumatoid agents used become, whereby they are characterised by a very low ulcerogene effect. These valuable pharmacological activities can become using standard methods certain.

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In the Writhing test at the rat, induced by Phenylchinon, e.g. points. that carprofene L lysinat (the compound of the appended example 1) a ED50 of 2,1 mg/kg p.o. up. Compared with this Lysinat the free acid, Carprofene, is and the sodium salt of it effect-moderate inferior, wise it nevertheless in the same test a ED50 of 8,6 and/or. 4,7 mgjkg up.

The acute toxicity (toxicity after unique oral administration at mice) amounts to 1250-2500 mg/kg for the mentioned above L-Lysinat as well as for the corresponding L-Argininat (the product of example 3).

The salts according to invention exhibit a very high bioavailability, in particular in the comparison with the corresponding free acid. So e.g. is. with rectal administration the bioavailability of carprofene L lysinat, measured in AUC (AREA more under the curve, the surface the bottom curve, which becomes obtained, if one lays the concentration on of the administered substance in the plasma against the time axis) more as 40% higher than from Carprofene.

The salts according to invention can as remedies, e.g.

in form of pharmaceutical preparations use find, which they contain vegetable oils, Po lyalkylenglykole and vaseline in mixture with, a pharmaceutical organic or inorganic inert carrier material, like water, suitable for the parenteral and in particular the enteric application, gelatin, gum Arabic, lactose, starch, magnesium

stearate, talc. The pharmaceutical preparations can in solid form, e.g. as tablets, dragee, capsules and in particular as suppositories; in semisolid form, e.g. as ointments; are present or in liquid form, e.g. as solutions, suspensions or emulsions. Ge.

gebenenfalls they are sterilized and/or contain Hilfsstof fe, like preservation, stabilization or emulsifying agent, salts for the change of the osmotic pressure or buffer. They can contain also still different therapeutic valuable fabrics.

The dosage can vary natural in each single case the individual circumstances within other boundaries and is to be adapted. Generally a daily dose from approximately 0.1 to 100 might be, preferably 1 to 10 mg/kg body weight appropriate with enteric administration. Single doses e.g. contain. about 20 to 500, vorzugswei SE 50 to 200 mg active substance.

Example 1
To a solution of 82,12 g (0.3 mol) Carprofene in 600 ml methanol is course-dripped a solution by 48,24 g L lysine (0.33 mol) into 150 ml waters. One agitates lasts to 1 hour. Then the solution at the rotary evaporator becomes concentrated to the Präzipitation begins so long (Badtemperx door 50). It will 3.5 1 ethanol (96%) added and it becomes on 4 °C cooled. After 2 hours filtered becomes. 115 g (to 91,3%) result rac-6-Chlor-a-methylcarbazol-2essigsäure-L-lysinat, Smp. 199-200 °C (Zers.)
Example 2
A solution of 10 g (0.0365 mol) Carprofene in 100 r methylene chloride/methanol (1: 1, v/v) becomes a solution of 5,34 g (0.0365 mol) DL lysine in 100 ml toluene added.

One agitates with blank during 1 hour, whereby a slow precipitation develops. After an other hour filtered becomes.

12.6 g (to 82%) result rac-6-Chlor-a-methylcarbazol2-essigsäure Dl-lysinat, Smp. 234.5 C (Zers.).

Example 3
A solution of 10 g (0.0365 mol) Carprofene in 100 ml methylene chloride/methanol (1: 1, v/v) becomes a solution of 6,36 g (0.0365 mol) L arginine in 400 ml methanol/water tetrahydrofurane (2: 1: 1, v/v/v) added. It becomes agitated during 1 hour with blank. The solution is again abdestilliert at the rotary evaporator complete concentrated, that residue with toluene staggered and the solvent. The residue is recrystallized from methanol/ether. One receives 15.5 g (to 94.6%) rac-6-Chlor-a-methylcarbazol 2-essigsäure-L-argininat, Smp 231.5 C (Zers.).

Example 4
In actual known manner galenische preparations the subsequent composition became prepared: a) Tablets
carprofene lysinat 153.4 mg
Pulverized lactose 124.6 mg
White corn starch 50.0 mg
Polyvinylpyrrolidone 10.0 mg
Carboxymethylstärke (sodium salt) 10.0 mg
Magnesium stearate 2.0 mg
350.0 mg b) capsules
carprofene lysinat 76.7 mg
Crystalline lactose 30.0 mg
Pulverized lactose 10.0 mg
White corn starch 27.3 mg
Talc 5.0 mg
Magnesium stearate 1.0 mg
150.0 mg C) suppositories on lipophilic basis
carprofene lysinat 153.4 mg
Fat-well-behaved matrix on Gly q.s. ad suppos.

zeridesterbasis I per adult.

d) Suppositories on hydrophilic basis
carprofene lysinat 115.1 mg
not ionogene emulsifiers up
Basis of PL glycol and q.s. ad suppos.

Polyoxyäthylen polyoxyprolylen I per adult.

Polymers

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CLAIMS

1. Salts of the 6-Chlor-a-methylcarbazol-2 acetic acid with a basic A-aminocarbonic acid.

2. Salts according to claim 1 the rac-6-Chlor-a-methylcarbazol 2-essigsäure with a natural occurring basic A-aminocarbonic acid, in particular with L lysine or L arginine.

3. The rac-6-Chlor-a-methylcarbazol 2-essigsäure-L-lysi nat as salt according to claim 2.

4. Method to the preparation of the salts according to claim 1, characterised in that one the 6-Chlor-a-methylcarbazol-2 acetic acid with a basic A-aminocarbonic acid in a solvent converts.

5. Pharmaceutical preparation on the basis of a salt after one of the claims 1-3.

6. Use of the salts after one of the claims 1-3 to the preparation of an anti-inflammatory, anti-rheumatoid and analgetischen agent.

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